

Research Paper

Calcium-Based, Antibiotic-Loaded Bone Substitute as an Implant Coating: A Pilot Clinical Study

N Logoluso¹, L Drago³, E Gallazzi¹, DA George², I Morelli¹, CL Romanò¹✉

1. Department of Reconstructive Surgery of Osteo-articular Infections C.R.I.O. Unit, I.R.C.C.S. Galeazzi Orthopaedic Institute, Milano, Italy
2. Department of Trauma and Orthopaedics, University College London Hospitals, London, UK
3. Laboratory of Clinical Chemistry and Microbiology, I.R.C.C.S. Galeazzi Orthopaedic Institute, Milan, Italy

✉ Corresponding author: Dr. Carlo Luca Romanò, Department of Reconstructive Surgery of Osteo-articular Infections, IRCCS Galeazzi Orthopaedic Institute - Via R. Galeazzi 4 20161 Milan, Italy. Phone: 00390266214743; Fax: 00390266214774; E-mail: carlo.romano@grupposandonato.it

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Published: 2016.10.01

Abstract

Background: Implant-related infections remain a major complication after orthopaedic surgery. Antibacterial coating of implants may prevent bacterial adhesion and biofilm formation. However, in spite of extensive preclinical research in the field, antibacterial coatings to protect orthopaedic implants in the clinical setting remain particularly few. The aim of the present study is to evaluate the safety of a calcium-based, antibiotic-loaded bone substitute as an antibacterial coating of cementless joint prosthesis.

Methods: From March 2013 to August 2015, 20 consecutive patients scheduled for cementless or hybrid two-stage revision surgery for peri-prosthetic joint infection were included in this prospective, observational, pilot study. Cerament G or Cerament V, a gentamicin or vancomycin-loaded calcium-based resorbable bone substitute (60% calcium sulphate, 40% hydroxyapatite), was applied at surgery on the stem surface of hip (n=7) or knee (n=13) revision prosthesis. After surgery, all patients underwent clinical (HHS or KSS and SF-12 score), laboratory and radiographic evaluation at 3, 6 and 12 months and yearly thereafter.

Results: At a minimum of 12 months follow-up, 19/20 (95%) patients showed no recurrence of infection and no signs of radiographic loosening of the stem. No adverse events were associated with the use of Cerament G or V.

Conclusions: This is the first pilot clinical study on the short-term safety of using a calcium-based, gentamicin or vancomycin-loaded bone substitute as a surface coating on cementless prosthetic implants. If confirmed by larger studies and at longer follow-ups, these findings may open a new perspective to protect intra-operatively orthopedic implants from bacterial adhesion, through the use of resorbable, osteoconductive, antibiotic carriers.

Key words: Peri-prosthetic infection; Coating; Calcium sulphate; Hydroxyapatite.

Introduction

Periprosthetic joint infection (PJI) remains one of the most feared complications after orthopaedic surgery [1]. Factors that are associated with an increased risk of post-surgical infection include the presence of an implanted biomaterial [2], while host's related factors, such as diabetes, renal failure, peripheral vasculopathy and smoking, may raise the

risk by more than 20 times, compared to the general population, in spite of current antibiotic prophylaxis [3].

The ability of microorganisms to adhere to the implant and to immediately produce a protective biofilm layer is currently considered one of the main reasons why the treatment of implant-related

infection remains particularly challenging [4, 5, 6]. As a result, any strategy aimed at protecting the implant at the time of surgery, to prevent bacterial adhesion and biofilm formation on the implant surface, can be extremely helpful in reducing PJIs, especially in high risk patients [7-9].

In the last decade, several synthetic calcium-based bone substitutes have been developed to deliver various local antibiotics [10, 25], and represent an established valid alternative to autologous or allograft bone grafts as a method to treat bone loss [11]. Among the several advantages, compared to bone grafts, synthetic bone substitutes offer unlimited availability, avoid donor site morbidity, and provide immediate mechanical support and osteoconduction to fill bone defects [12]. Moreover, they may be pre-loaded with antibiotics, thus acting as local antibacterial carriers. Antibiotic impregnation allows high local concentration of antibiotics, limiting systemic side effects and ensuring the delivery of antibiotic where needed in a way that is not dependent on vascular supply [13, 14].

Cerament (BoneSupport AG, Lund, Sweden) is an injectable bone substitute, composed of 60% w/w fast resorbing calcium sulphate, which is intended to be quickly replaced by newly formed bone, and 40% w/w of calcium hydroxyapatite, that acts as a long-lasting scaffold to allow further bone ingrowth [15]. Cerament G and Cerament V incorporate gentamicin sulphate (175 mg/10 mL) and vancomycin (66 mg/mL), respectively, and preclinical studies

have demonstrated their efficacy in treating infected bone defects [16] and no detrimental effects on osteointegration when used as a coating on implants [17].

The aim of the present prospective, observational pilot clinical study was to evaluate the use of Cerament G or Cerament V applied intra-operatively as a coating of cementless joint prosthesis, in order to provide additional local antibacterial protection, without interfering with implant osteointegration.

Materials and Methods

From March 2013 to August 2015, 20 consecutive patients scheduled for two-stage hip or knee prosthesis reimplantation for PJI or septic osteoarthritis, were included in this single center, prospective, observational study (Table 1). Inclusion criteria were the need for joint reimplantation using a cementless or hybrid revision prosthesis, and previous infection caused by microorganism(s) sensitive to gentamicin or vancomycin. Exclusion criteria were the need of a fully cemented joint prosthesis, psychiatric or neurological disorders, pregnancy or breastfeeding at the time of surgery and hypersensitivity to aminoglycosides. Our local Ethical Committee approved the study. All patients were informed and gave their consent to participation to this study.

Table 1. Demographics, pre-clinical data, diagnosis, surgical procedures and results of included patients.

N.	Sex	Age	Relevant co-morbidities	Diagnosis	Primary Organisms	Cerament G or V	Follow-up (months)	Outcome	Complications	Adverse Events	SF12 (P +M)	KSS	HHS
1	F	78	Type 2 diabetes	TKA infected	Streptococcus Gallolyticus	Cerament G	36	No infection		None	85,6	86	NA
2	F	65	None	THA infected	None Isolated	Cerament G	34	No infection	None	None	96	NA	88
3	M	89	None	THA infected	Staphylococcus Epidermidis	Cerament G	32	No infection	None	None	90,5	NA	91
4	F	77	Chronic renal insufficiency Congestive heart failure	THA infected	Staphylococcus Epidermidis	Cerament G	30	No infection	Heterotopic ossification (Brooker grade II)	None	88	NA	81
5	F	71	None	TKA infected	None Isolated	Cerament G	29	No infection	None	None	95	76	NA
6	F	59	Thyroiditis	THA infected	Paenibacillus Spp. MS	Cerament G	29	No infection	None	None	99,7	NA	86
7	F	71	Type 2 diabetes	THA infected	Stenotrophomonas spp	Cerament G	28	No infection	None	None	87,3	NA	70
8	M	71	Type 2 diabetes	TKA infected	Staphylococcus Aureus	Cerament G	24	No infection	None	None	90,8	86	NA
9	F	88	None	TKA infected	None Isolated	Cerament G	20	No infection	None	None	84	72	NA
10	F	65	None	Septic knee osteoarthritis after exposed proximal tibia fracture	Pseudomonas Aeruginosa	Cerament G	20	Infection	Surgical wound dehiscence	None	69,1	64	NA
11	M	51	None	TKA infected	None Isolated	Cerament G	12	No infection	None	None	98	85	NA
12	M	40	None	TKA infected	Staphylococcus Epidermidis	Cerament V	12	No infection	None	None	100	80	NA
13	F	49	None	THA infected	Staphylococcus Aureus	Cerament V	12	No infection	None	None	88	NA	80
14	F	68	None	THA infected	Staphylococcus Lugdunensis	Cerament V	12	No infection	None	None	90,5	NA	82,6
15	F	77	Bradiarrhythmia, Psoriasis	TKA infected	Enterococcus Faecalis Escherichia Coli Staphylococcus Aureus	Cerament V	12	No infection	None	None	77,2	77	NA

16	M	68	Prostatic cancer with bone metastasis	TKA infected	Staphylococcus Epidermidis Staphylococcus Lentus Enterococcus Casseliflavus Group D	Cerament V	12	No infection	None	None	73,8	72	NA
17	F	70	None	TKA loosening	None Isolated	Cerament G	12	No infection	None	None	87,7	80	NA
18	M	63	Hypertension, ischemic heart disease	TKA infected	None Isolated	Cerament V	12	No infection	None	None	80	75,5	NA
19	M	81	None	TKA infected	None Isolated	Cerament G	12	No infection	None	None	76	75	NA
20	M	57	Hyper tension, Type 2 diabetes	Septic non union distal femur and knee septic osteoarthritis	Staphylococcus capitis	Cerament V	12	No infection	None	None	77	77	NA

All patients underwent a first stage procedure, including removal of all foreign infected material and complete debridement of bone and soft tissues, followed by implantation of a preformed hip or knee gentamicin-loaded spacer (Spacer G or Spacer K, Tecres SpA, Sommacampagna, Italy). During surgery, four to six samples of periprosthetic tissue were collected from different sites. Solid tissue samples from periprosthetic tissue were placed into sterile cases, and were subsequently cultured in anaerobic and aerobic agar media and in thyoglycolate broth enriched with vitamin K and hemin. After an incubation time of ten days, positive cultures were sent for organism identification and sensitivity testing.

After an interval period ranging from 8 to 12 weeks, all patients underwent revision surgery with a hip (A-Aeque, AdlerOrtho Srl, Milan, Italy) or knee (TC3, DePuy Inc., Warsaw, USA or Endomodel, Waldemar-Link GmbH, Hamburg, Germany) revision prosthesis.

At the time of implantation, the prosthetic stem and cup (for hip prosthesis) was fully coated using 10 to 20 mL of Cerament G or Cerament V (Figure 1). Cerament was prepared according to manufacturers guidelines during the surgical procedure. Four minutes after the completion of the preparation process, Cerament was directly applied with a disposable syringe onto the surface of the prosthesis stem, which was immediately implanted according to our standard practice. The hip prostheses were completely cementless, whilst the epiphyseal part of the knee implants were secured with a tobramycin-loaded bone cement (Simplex, Stryker Inc., Mahwah, NJ, USA).

Follow-up consisted of clinical, laboratory and radiographic examination at approximately 3, 6 and 12 months after surgery and yearly thereafter. The average follow up time was 18.1 months \pm 6.7 (range 12-36).

Harris Hip Scores (HHS) or Knee Society Scores (KSS), and short form (SF)-12 were collected at every

follow-up visit. Recurrence of infection, defined as the presence of clinical signs of inflammation/infection at the surgical site and an elevation of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) serum levels, was recorded.

Radiographic bone healing, the presence of radiolucent lines, and implant loosening were monitored at follow-ups by an independent radiologist; local or systemic clinical side effects or the need for unplanned further surgery were also recorded.

Results

A total of 20 patients (8 males, 12 females) were included in the study. The mean age was 67.8 years old (range 40 – 89 years). Each patient completed a minimum follow up of 12 months (maximum 36 months, mean follow up 18.1 months \pm 6.7). Microbiological data with isolated organisms and antibiotic regimen are reported in Table 1, together with KSS or HSS scores, SF-12 evaluation, infection recurrence and adverse effects.

At the latest follow-up, there was no clinical or laboratory evidence of infection recurrence in 19 patients (95%) and no radiographic signs of implant loosening (cf. Figure 2). In particular, non progressive radiolucent lines were observed in two patients (2 and 3) with hip prosthesis in Gruen zone 1 and 7. No detectable subsidence of the implants was detected at the latest follow-up.

No adverse events were associated with the use of Cerament G or V.

Infection recurrence occurred in patient number 10. She was a 65 year old woman affected by a severe septic knee osteoarthritis, caused by *P.aeruginosa* after an exposed proximal third tibia fracture with associated extensive soft tissue damage and multiple scars. Following a two-stage knee joint prosthesis, with a Cerament G coated implant, she developed a skin necrosis with wound dehiscence that required early surgical debridement with partial revision of the

prosthesis and a muscle flap. At the latest follow-up, she has a persistent small fistula, controlled by

suppressive antibiotic treatments and she refused further surgery.

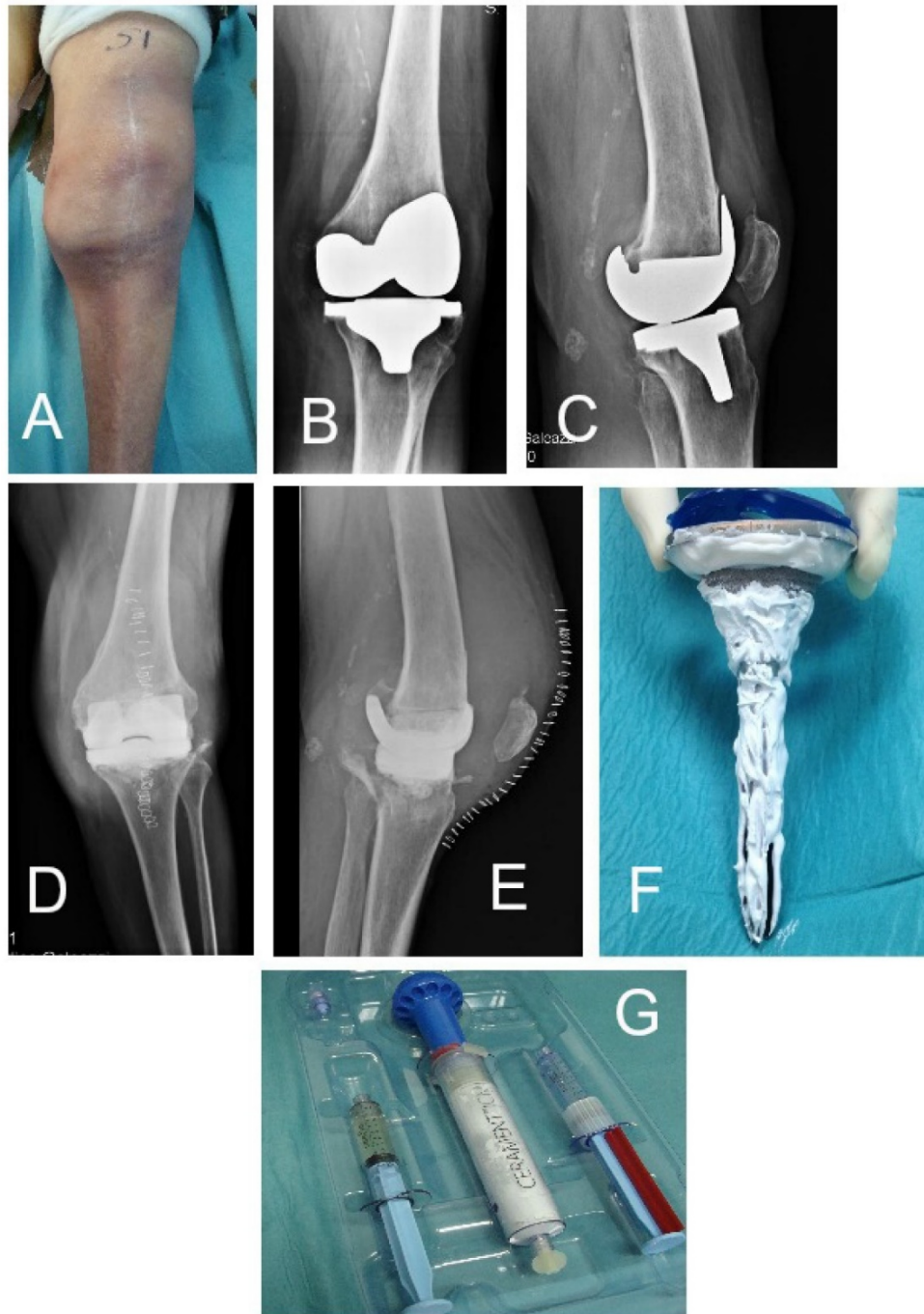


Figure 1. Patient n. 3 (see Table 1). (A) pre-operative clinical aspect, (B,C) pre-operative radiographic findings with implant loosening and osteolysis and (D,E) after antibiotic-loaded spacer implanted. (F,G) Cerament G preparation kit and the coated implant at the time of reimplantation.

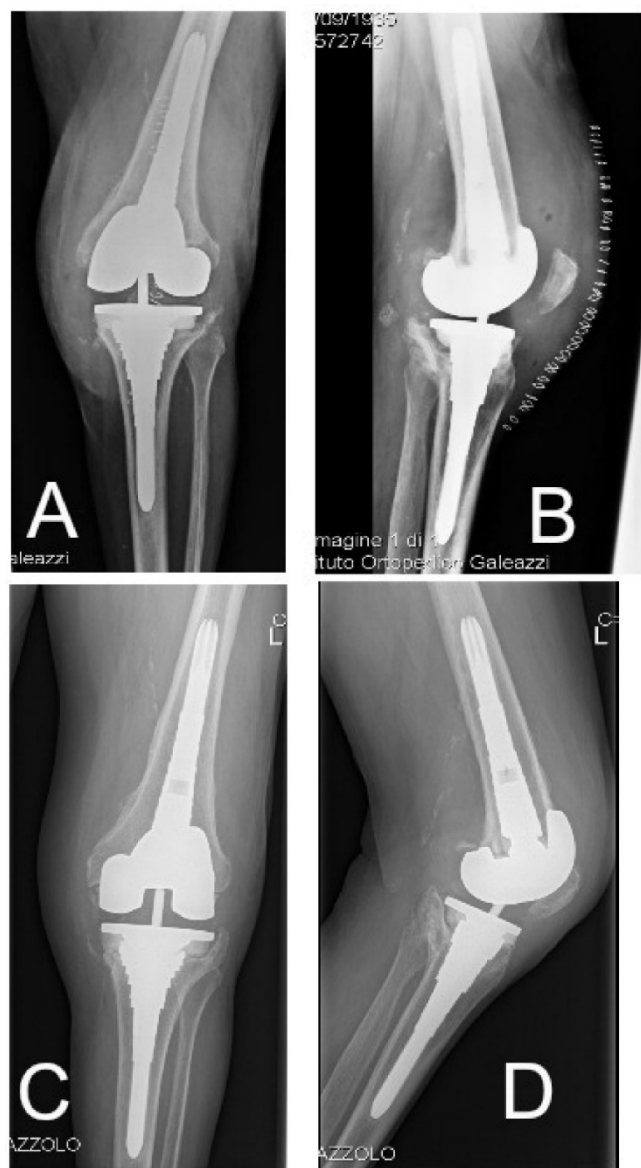


Figure 2. Plain radiographs of the same patient described in Figure 1 immediately after surgery (A,B), at 12 months (C,D).

Discussion

To our knowledge, this is the first study reporting the use of a calcium-based, antibiotic-loaded bone substitute used as a coating on cementless or hybrid joint implants. It is well recognized that implant features, including size, shape, material and surface finishing play an important role in the onset or prevention of PJI [18]. Several antibacterial coating technologies are currently under review, but only few are currently commercially available for clinical use [9, 25].

Allogenic antibiotic-loaded cancellous bone graft has been shown to be effective for delivering local antibiotics when used during total joint arthroplasty [20]. However, their limited availability, risk of

disease transmission and costs prevent more widespread use of this resource. To overcome these limitations, various synthetic bone substitutes have been introduced to the market,[21-24] but their application as a coating on implants has not been previously reported.

Cerament was developed as an injectable bone substitute, acting both as a temporary filler and a scaffold for bone remodeling [15]. In a recent study, Cerament was used as a filler in tibial plateau fractures, showing satisfactory radiological and clinical outcome with a mean follow up of 44 months. However, the presence of infection was an exclusion criteria in this study [26].

Cerament G and Cerament V, the more recently available version of Cerament, can be utilized in septic bone defects, providing local antibiotic elution with a peak level in the first 3 hours and sustained release above minimal inhibitory concentration (MIC) for up to 28 days. [BoneSupport data on file] The semi-liquid formulation, that lasts several minutes after the preparation process before hardening, enables it to be easily spread onto a surface.

This pilot study has shown for the first time that Cerament G or V can be safely applied at the time of orthopaedic surgery as a coating on a cementless or hybrid implant. However, our findings do have some limitations; histological analysis was not undertaken to confirm osteointegration of the coated implants, nor were microbiological investigations performed to assess the ability of the Cerament G or V to prevent bacterial adhesion and biofilm formation when acting as a coating. There is a need for a larger, prospective, comparative study to further analyze its efficiency, with a longer follow-up.

Conclusions

This is the first pilot clinical study on the short-term safety of using a calcium-based, gentamicin or vancomycin-loaded bone substitute as a surface coating on cementless and hybrid prosthetic implants. Our data, although in a limited case series, demonstrates the safety of this application with promising results in infection prevention. If confirmed by larger studies, these findings may open a new prospective to protect intra-operatively orthopedic implants from bacterial adhesion, through the use of resorbable, osteoconductive, antibiotic carriers.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki

declaration and its later amendments or comparable ethical standards

Competing Interests

The authors have declared that no competing interest exists.

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